Management of pain in sickle-cell disease

Iheanyi Okpala MRCPath FWACP Adel Tawil MBBS MRCP

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The acutely painful episodes that characterize sickle-cell disease were described in 1872 by Africanus Horton[1], though the mechanism remained uncertain until, nearly thirty years later, James Herrick observed the sickling deformity of red cells that causes vaso-occlusion and tissue infarction.

Sickle-cell disease (SCD) is the commonest globin gene disorder: across the world, about 300 000 children are born with it each year[3]. The pain of sickle-cell crisis is excruciating and, in global terms, a major health problem.

TYPES OF PAIN IN SICKLE-CELL DISEASE

Pain caused by sickle-cell disease can be acute, chronic or a mixture of the two. The acute pain of tissue infarction, in skeletal or soft tissue, tends to be sudden, unpredictable in onset and intense. After resolution of sickle-cell crisis, it usually stops. Chronic pain in SCD is not simply a continuation of the pain of vaso-occlusion: it is usually secondary to avascular necrosis of bone at various joints—the hips, shoulders and ankles, in decreasing order of frequency. Also, avascular necrosis commonly develops in the spine, causing chronic back pain and displaying the well-known 'fish-mouth' appearance on X-rays. The knees are seldom involved. Individuals with SCD are not, of course, immune to other painful acute and chronic disorders unrelated to the haemoglobinopathy. Abdominal pain may be a manifestation of sickle-cell crisis affecting the abdominal viscera, but it may also reflect a surgical emergency such as perforation. Similarly, chronic joint pain in people with SCD can be caused by rheumatoid arthritis, osteoarthritis or other forms of degenerative joint disease: one memorable individual turned out to have tuberculous arthritis in one hip and avascular necrosis in the other. In a person with a previously recognized cause of chronic pain such as hip necrosis, acute exacerbations can result either from new vaso-occlusive events in the same site or from movement-induced injury to the damaged joint. Previously satisfactory measures for pain relief may then become inadequate. Somewhat easier to recognize and manage is the development of generalized painful crisis in an individual who formerly had chronic pain at one or few anatomical sites. Resolution of a crisis requires a switch away from medications that are suitable only for the relief of acute pain.

TREATMENT OF ACUTE PAIN

The methods of pain relief in SCD depend on whether the pain is acute, chronic or a mixture of the two types and on whether the patient is opioid-naïve or opioid tolerant. The guiding principle is to use a stepwise approach, akin to that used for hypertension. When the patient has not been seen before, he or she can be asked what types and doses of analgesics have in the past been effective; but a pitfall of this approach is that people with drug-seeking behaviour may exaggerate the intensity of their pain or the effective doses of analgesics so as to obtain more medication. Our protocol for treating acute (crisis) pain caused by SCD is summarized in Table 1. Regular analgesia is given for acute pain. The standard dosing interval for morphine injections and rapid release preparations is 4–6 hours, but we find that some individuals become so tolerant to opioids that doses are needed 2-hourly. Every effort is made to prevent such tolerance developing in new patients because there is a limited choice of injectable opioids that can be used in acute painful episodes. By combining analgesics with different mechanisms of action, such as paracetamol or diclofenac, the dose of opioids can be kept to a minimum.

The non-steroidal anti-inflammatory drugs (NSAIDs) are effective in relieving the inflammatory component of infarctive (vaso-occlusive) bone pains. Diclofenac by mouth, 50 mg three times daily or 75 mg twice daily, is added to the analgesic regimen if the patient has no

Table 1 **Treatment of acute pain**

Severity	*Opioid naïve*	*Opioid tolerant*
Mild/ moderate	Dihydrocodeine tablets 30 mg/4 h *or* co-codamol 2 tablets/4 h *or* co-proxamol 2 tablets/4 h	Immediate-release morphine sulphate tablets 10–40 mg/4 h *or* hydromorphone tablets 1.3–3.9 mg/4 h
Severe	Diamorphine 2.5–5 mg/4 h s.c.	Diamorphine 10–20 mg/2–4 h s.c.

Diclofenac or ibuprofen added for bone pains if no contraindications
s.c.=Subcutaneous

Haematology Department, St Thomas' Hospital, London SE1 7EH, UK
Correspondence to: Dr I E Okpala

Table 2 **Equivalent doses of opioids**

		Ratio
Subcutaneous diamorphine 400 mg/24 h	Oral immediate release morphine sulphate 130 mg/4 h	1:2
Oral immediate-release morphine sulphate 130 mg 4-hourly	Oral slow-release morphine sulphate 400 mg twice daily	1:1
Oral immediate-release morphine sulphate 130 mg 4-hourly	Subcutaneous diamorphine 400 mg/24 h	2:1
Oral dihydrocodeine 30 mg 4-hourly	Oral immediate-release morphine sulphate 3 mg 4-hourly	12:1

contraindications such as peptic ulcer, asthma or renal impairment. For those who are vomiting or cannot take the drug orally, diclofenac by suppository (100 mg daily) is an alternative. One complication of SCD is nephropathy—characterized by proteinurea, ranging from microalbuminuria to massive excretion (with nephrotic syndrome)[4,5]. The nephropathy can be worsened by NSAIDs, so treatment with these agents should be stopped after a week at the most. Patient-controlled analgesia (PCA) is reported to be as safe and effective as intermittent opioid injections[6], and in our centre PCA consists of diamorphine subcutaneous infusions. PCA is used for patients who prefer it to intermittent injections.

If pain is not controlled, the amount of opioid is increased in small increments (e.g. diamorphine 2–3 mg) to avoid the risk of central nervous system depression. When the acute pain begins to resolve, the dose is tailed off gradually rather than stopped abruptly, so as to avoid withdrawal symptoms, which can mimic those of sickle-cell crisis. These strategies apply to intermittent injections or oral administration of opioids, not to PCA. In patients started on diamorphine less than 10 mg/injection, the opioid is stopped when the crisis resolves. If intermittent injection is started with a dose more than 10 mg a switch from parenteral to oral analgesics is made when the dose of diamorphine is less than 10 mg per injection. The equivalent doses of other opioids are shown in Table 2. In deciding the dose to be prescribed, one should be guided by the degree of opioid sensitivity observed clinically in the patient. If the prescribed dose is based solely on the theoretical equivalent amounts, an individual who is very sensitive to opioids runs a risk of overdosage, with respiratory depression.

Diamorphine has replaced pethidine as the analgesic of first choice for acute pain in SCD. Of about 800 adults with the haemoglobinopathy who receive treatment in our centre, only 3 (who reacted seriously to diamorphine) still receive pethidine. There are several reasons for preferring diamorphine. The pethidine metabolite is excitatory to the nervous system, and causes seizures. Diamorphine has a longer duration of action, and mass for mass is a more potent analgesic. Whereas diamorphine is soluble enough to be given subcutaneously, pethidine has to be injected into muscle. Repeated intramuscular injections of pethidine cause muscle fibrosis and contractures; absorption from the injection site becomes less and larger doses are needed—causing further muscle fibrosis and, far more serious, increasing the likelihood of drug dependence or addiction.

When opioids are used as part of pain management in SCD, their side-effects must be prevented or treated. Constipation is treated with agents such as sodium docusate 100 mg three times daily, lactulose 10–15 mL twice daily or senna 2–4 tablets daily. Nausea/vomiting can be relieved with metoclopramide 10 mg or cyclizine 50 mg 8-hourly, orally or by injection. Many of our patients get pruritus when given morphine, and this commonly responds to oral hydroxyzine 25 mg twice daily. Pruritus does not imply allergy to morphine and does not warrant stopping the drug or switching to pethidine. We find that pruritus is more frequent in black patients than in other ethnic groups. The most serious side-effect of opioids is respiratory depression, which sometimes requires treatment with an opioid antagonist such as naloxone.

TREATMENT OF CHRONIC PAIN

In our centre, the approach to chronic pain caused by SCD is multidisciplinary, including the use of analgesic drugs, nerve block, physiotherapy, orthopaedic intervention or surgery, and cognitive behaviour therapy. Mild chronic pain is relieved by dihydrocodeine or co-proxamol (dextropropoxyphene/paracetamol). Any pain not controlled by two tablets 4-hourly is considered moderate/severe, and we then step up to morphine. Slow-release oral morphine, taken 12-hourly, is used for long-term analgesia, with smaller amounts of rapid-release oral morphine for breakthrough pain. The alternatives are slow-release and rapid-release hydromorphone. For the reasons given earlier, we discourage long-term use of NSAIDs for chronic pain in SCD. A switch from morphine to hydromorphone, or vice-versa, is made when tolerance develops to one or other drug; tolerance (the need for increasing doses to maintain the same effects) is a feature of long-term opioid therapy.

In a patient whose chronic pain is severe enough to warrant opioid therapy, supplementary approaches may be applicable. For example, the pain of avascular necrosis of the hip, shoulder or intervertebral joints can be lessened by

Box 1 **Nerve block for chronic hip pain**

A man aged 23 with sickle-cell disease complicated by avascular necrosis of the left femoral head developed methicillin-resistant *Staphylococcus aureus* (MRSA) infection of the left hip joint after left femoral osteotomy. Wound healing was delayed and he continued to have chronic hip pain uncontrolled with opioids. Further surgery was judged inadvisable because of the likelihood of reactivating MRSA infection. Left hip nerve block, performed by anaesthetists, yielded profound benefit and allowed effective pain relief with hydromorphone 16 mg twice daily. A repeat nerve block was required after 4 months to maintain analgesia.

nerve block, with benefit lasting up to 12 weeks for each injection (Box 1). Physiotherapy can lessen joint pain, prevent muscle contracture and lessen joint stiffness and physical disability. Cognitive behaviour therapy helps the individual to develop strategies for coping with pain and other psychological disturbances caused by SCD[7]. Orthopaedic devices for back support, or for raising the foot to make up for differences in length between the legs, help reduce chronic pain in the hips or back. In some cases of avascular necrosis, orthopaedic surgery is the only treatment that effectively relieves pain, and should be performed as early as possible. For other orthopaedic procedures such as total hip replacement, the duration of benefit is limited[8] and there is a strong argument for deferring operation until the pain becomes intolerable.

DEPENDENCE AND ADDICTION

Unfortunately, opioid therapy can lead to dependence or addiction. Dependence—the occurrence of an abstinence syndrome (withdrawal) after abrupt reduction in the dose of a drug or after administration of an antagonist—can develop after just a few days of repeated administration. More serious is addiction—a psychological and behavioural syndrome in which there is craving for a drug, compulsive use, and strong tendency to relapse if the drug is withdrawn. Addiction affects only a small percentage of SCD patients[9,10]. Out of about 800 adults with SCD registered in our centre, only 4 have been addicted to opioids. However, such patients do take a disproportionate amount of time and resources.

Healthcare personnel have a duty to ensure effective relief of pain—which is broadly defined as an unpleasant sensation and emotional experience that occurs in association with actual or potential damage to part of the body. In the absence of objective measures, assessment must be based on what the patient says. However, they must also be alert to the possibility that prescriptions of opioids or other addictive drugs such as temazepam exceed the medical needs of an individual. Pointers to dependence are a patient's insistence on determining the dose and timing of an addictive drug without caring as much about antibiotic or other therapy, incessant objections to dose reduction considered medically appropriate, and frequent demands for dose increases especially after working hours. An addicted person may acquire drugs illegally, or unlawfully obtain materials used for drug injection. Also, an occasional SCD patient who is neither dependent nor addicted will dispose of prescribed drugs for personal gain. One strategy to obtain excess supplies is to register with more than one general practitioner or hospital; another is to use different personal details such as name, address or date of birth.

If dependence or addiction is in the differential diagnosis, referral to a drug dependency unit is advisable. Healthcare personnel should prescribe only the amounts of drug they judge necessary for control of pain.

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